REMARKS

With entry of this amendment, claims 1-42 are pending in the application. By this amendment, claims 3, 13, and 16-42 have been amended and/or renumbered for clarity in accordance with the Examiner's suggestions. The amendments herein are fully supported by the disclosure, and no new matter has been added to the application. Entry of this amendment, and reconsideration of the application in view of the remarks below, are respectfully requested.

Claim Objections

In accordance with the Examiner's observation that the original claim numbering was in error, wherein claim numbers 15 and 16 were repeated. Originally misnumbered (second occurrence) claims 15-16, and the following misnumbered claims 17-40 below, have been collectively renumbered as claims 17-42, respectively. Applicants acknowledge that the references to claim numbers presented in the Office Action are provided in reference to the correct claim designations as renumbered herein, and the following remarks are addressed accordingly.

Patentability Under 35 USC § 112

Claims 3, 14, 20, 31 and 37 are rejected under 35 USC § 112, first paragraph, for alleged lack of enablement. The central factual basis for this rejection asserted by the Office is that the disclosure allegedly "does not disclose the AUC for the intramuscular dose" to support Applicants' claims to a solution of cyanocobalamin providing "a bioavailabilty of cyanocobalamin, when administered nasally, of at least about 7% relative to an intramuscular injection of cyanocobalamin". (see, e.g., Office Action at pp. 8-13).

Applicants respectfully traverse the foregoing grounds for rejection and submit that the instant disclosure fully enables the subject matter set forth in the pending claims.

Applicants concede the Office's point that explicit AUC data are not provided for bioavailability of cyanocobalamin delivered via intramuscular injection. However, the subject data are directly derivable from comparative data provided in the application,

which fully support the subject, "at least 7%" relative bioavailability functional limitation recited in Applicants' claims.

As a preliminary point, Applicants' specification clearly discloses that the cyanocobalamin solutions of the invention, when administered intranasally, achieve "bioavailability of at least 7% of the bioavailability of an intramuscular injection of cyanocobalamin." (see, e.g., page 3, lines 22-23). Consistent with this teaching, the disclosure further teaches that in certain embodiments the said minimum 7% bioavailability compared to intramuscular injection is "at least 8%, more preferably at least about 9, 10, 11, or 12%".

These positive assertions regarding enablement rendered in Applicants' disclosure are entitled to a presumption of correctness. As explained in the PTO's Enablement Guidelines, (see, e.g. Example 5E: "Peptides for Treating Obesity," at page 46):

> The Office must accept as being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence, to question them.

Thus, the Office has the initial burden in this case to provide factual evidence that is "inconsistent" with Applicants' assertions regarding enablement. In re Marzocchi et al., 169 USPQ 367 (CCPA 1971). Applicants respectfully submit that no such factual evidence has been provided in the Office Action.

Applicants' disclosure, however, does not merely present positive assertions supporting enablement of the pending claims. In fact, detailed comparative bioavailability studies and results are presented in the Examples that clearly and comprehensively support this aspect of the invention.

As presented, for example, at page 17, under the heading "PHARMACOKINETIC RESULTS":

> The relative bioavailability for the two IN formulations was 0.9715. Bioavailability when comparing treatment A (Spray) versus treatment C (IM) was 0.6105, and 0.6284 when comparing Treatment B (gel) versus Treatment C (IM).
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> The pharmacokinetic profiles of the spray formulation and the gel formulation are similar for Cmax (1480 pg/mL, 1670 pg/mL, respectively) and AUC_{0-t} (9200 pg*hr/mL, 9700 pg*hr/mL, respectively). Additionally, the median difference for Tmax between the spray and gel IN formulation was less than 15 minutes (-0.24). The C_{max} value for the IM formulation was significantly higher than the C_{max} values for the two IN formulations ($p<0.0001$).

Despite that these data do not expressly provide comparative AUC values for IM biovailability of cyanocobalamin from Applicants' studies, these values are readily and accurately derivable from the data that are presented. In particular, the comparative bioavailability study results presented above demonstrate that the "relative bioavailability" ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. These values represent ratios of the natural log of geometric means of the AUC based on nominal doses (see, e.g., page 17). These data were dosed normalized according to conventional practice to the appropriate dose multiple based on a dose of 500 µg given intranasal and 100 µg given by IM (see, e.g., page 12).

The skilled artisan will readily comprehend these data and fully appreciate that the dose normalized data yield a ratio of bioavailability between Applicants' IN cyanocobalamin solution and IM-administration that reasonably corresponds to the claimed value of "at least about 7%". This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is 0.6105 X 100 µg/500µg X100 = 12%; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data likewise fully evince the corresponding AUC for the IM injected study comparator, according to Applicants' disclosure. For example, the arithmetic mean of the AUC for IM is calculated as 147155 pg*hr/mL (as readily derived by reverse mathematical operation from the ratios given--for example for the spray 92000/147155 = 0.62 ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability

value within Applicants' described range of at least 7% and preferably 9, 10, 11 or 12 % for the Spray versus IM.

In view of the foregoing evidence, the data provided in Applicants' disclosure fully support the subject matter pertaining to relative bioavailability presented in the pending claims. In this regard, enablement must be viewed by the Office from the standpoint of the skilled artisan, and it is improper to require that the disclosure correspond "precisely" to the language and scope of the claims. It is sufficient that the disclosure, as here, is "reasonably correlated" with the language and scope of the claims, and that skilled artisans would have been able to practice the invention without "undue experimentation." The record clearly evinces that these requirements are fully satisfied by Applicants' disclosure, on which basis the rejection of claims 3, 14, 20, 31 and 37 under 35 USC § 112 is respectfully submitted to be overcome.

Claims 17, 18, and 19 are rejected under 35 USC § 112, second paragraph, for alleged indefiniteness. The Examiner kindly advises that the subject claims make reference to the "method of claim 12", although claim 12 recites a "kit" and not a method. Appropriate corrections of these typographical errors are presented to claims 17-19 herein, thereby obviating the objection

Patentability Under 35 USC § 102

Applicants note for the record that the Office has substantively reviewed the application and pending claims and has not levied any rejection of claims under 35 USC § 102. On this basis Applicants understand that the Office has fully considered the pending claims and determined that the subject matter therein is novel over all publications and patents of record in the application.

Patentability Under 35 USC § 103

Claims 1-16 are rejected under 35 USC § 103(a) as allegedly unpatentable over Wenig (USPN 4,724,231), Grychowski et al. (USPN 6,745,760), Slot et al. (Gastroenterology 113:430-433, 1997), Garcia-Arieta et al. (Biol. Pharm. Bull. 24:1411-1416, 2001), and Harris et al. (J. Pharm. Sci. 77:405-408, 1988).

Wenig is apparently relied upon as the primary reference, which presumption Applicants have based on i) the order of presentation of references in the formal statement of rejection by the Office (above), and ii) on the basis of how the rejection arguments are presented by the Office. In particular, the principal focus of the Office Action relates to comparison of Applicants' cyanocobalamin formulations to the disclosure Wenig in view of Garcia-Arieta et al. and Slot et al: (Office Action at pp. 3-8). Consistent with this understanding, the Office asserts at page 5 that it would allegedly have been obvious to employ "drug delivery devices and parameters for adjustment to optimize formulations and formulation ingredients" (underscore added). These comments clearly indicate that the rejection proposes modification of a cyanocobalamin formulation as allegedly taught by Wenig in view of Garcia-Arieta et al. and Slot et al. (see below) to yield a kit according to Applicants' claims--by employing devices and parameters as allegedly taught by Grychowski et al. and Harris et al. Similarly, the Office Action asserts at page 6 that:

> Obviousness based on similarity of formulation and function to those ingredients of the formulation entails motivation to make the claimed kit in expectation that compounds similar in formulation will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compositions in searching for new formulations of cyanocobalamin.

Based on the foregoing, Applicants will address the stated grounds for rejection with the presumptive construction that Wenig is relied upon by the Office as the primary reference, and that the Office proposes two distinct combinations. i.e., a first combination of Wenig as allegedly suggested to be modified by Garcia-Arieta et al. and Slot et al. to yield a proposed cyanocobalamin formulation; and a second combination combining this allegedly obvious formulation with "devices and parameters" allegedly taught by Grychowski et al. and Harris et al. Accordingly, the first, formulation composition will be addressed initially below, followed by a discussion of the proposed "devices and parameters" combination.

If Applicants understanding of the construction of the rejection is in error, further clarification of the rejection by the Office is earnestly solicited.

With regard to cyanocobalamin formulation teachings, the Office cites extensively to Wenig, as the presumptive primary reference (Office Action at pp. 4-5), for allegedly teaching:

> A pharmaceutical composition comprising cyanocobalamin and water with no mercury for intranasal administration (see Examples 1-3) with a viscosity that can be adjusted to below 1000cPs (see column 3 lines 1-5 where Wenig states that the important point is to use an amount which will achieve the selected viscosity) and has a similar bioavailability to that of a gel formulation (see Applicant's specification pp. 17-18); where the solution contains citric acid and sodium citrate with a pH of about 5 (see column 2 lines 52-58 and example 3); where the composition contains humectants such as sorbitol, propylene glycol and glycerine with the glycerin present at a concentration of about 2.23% (see column 3 lines 10-13 and example 1A and 1C); where a preservative is present such as benzyl alcohol, chlorobutanol and benzalkonium chloride with the benzalkonium present at a concentration of about 0.02% (see lines 26-30 and example 1B) and where solution contains an optimized formulation with 0.5% cyanocobalamin present, 0.12% citric acid and 0.32% sodium citrate all present as a percent of total weight (see example 1C and 3) and where the optimized formulation . . . is suitable for intranasal administration (see example 2).

The Office concedes that "Wenig does not teach a formulation that is in aqueous form", and "also does not teach the intranasal formulation in the same format as applicant" (Id.)

The Office further relies upon Garcia-Arieta et al. as a secondary reference, for allegedly teaching proposed modifications of Wenig directed to "the nasal administration of cyanocobalamin in nasal solution (spray and drops) as well as the bioavailability of this formulation (see p. 1412 second column under nasal bioavailability studies p. 1415 figure 4 and table 2)."

Slot et al. is also relied upon as a secondary reference, for allegedly teaching "an intranasal formulation of hydroxocobalamin preserved solution".

Applicants respectfully traverse the foregoing grounds for rejection and submit that the invention set forth in the instant claims, recognized by the Office as novel over the art of record as noted above, is neither disclosed nor practically suggested by the cited references viewed in combination as advocated by the Office.

As noted above, the Office principally relies upon Wenig to support the instant rejection, and specifically asserts that this primary reference discloses a "cyanocobalamin and water" formulation for intranasal administration "with a viscosity that can be adjusted to below 1000 cPs." The only evidence offered to support this critical alleged teaching relating to viscosity is that Wenig allegedly "states that the important point is to use an amount which will achieve the selected viscosity" (Office Action, at p. 3).

Applicants respectfully disagree with the Office's interpretation of Wenig--particularly with respect to the alleged teaching by Wenig to employ an "adjusted" or "selected" viscosity for an intranasal cyanocobalamin formulation "below 1,000 cPs". Contrary to the Office's construction, Wenig unambiguously teaches away from intranasal cyanocobalamin formulations having a viscosity below Wenig's expressly-stated, critical range of 2500-6000 cPs. The Office improperly ignores this critical range expression. In fact, the citation provided by the Office to allegedly support an "adjusted" or "selected" viscosity within Applicants' claimed range (cited as column 3 lines 1-5 of Wenig) is taken out of context. Rather than teaching or suggesting viscosity adjustment "to below 1000 cPs", the subject passage in Wenig expressly states that an intranasal cyanocobalamin formulation "will contain a sufficient amount of a thickening agent so that the viscosity is from about 2500 to 6500 cps, although *more viscous compositions even up to 10,000 cps may be employed*." (Col. 2, lines 37-39, emphasis added). Nowhere does Wenig teach or suggest adjustment or selection to lower viscosity of an intranasal cyanocobalamin formulation to even approach Applicants' disclosed range. On the contrary, artisans of ordinary skill would immediately interpret Wenig's disclosure as teaching directly away from the instantly claimed intranasal cyanocobalamin formulations having a viscosity less than about 1000 cPs. Wenig's disclosure expressly indicates that intranasal cyanocobalamin compositions have a vastly higher viscosity than this, in all embodiments contemplated. Thus, Wenig teaches that

"[a] typical composition of this invention" has a viscosity of "about 4500 cps" (Col. 3, lines 41-51). Perhaps more significantly, each of the working embodiments provided by Wenig (for which viscosity values are provided, and which were reportedly validated in terms of bioavailability by measurement of blood plasma cyanocobalamin levels), have respective viscosities of 4000 cps, 3500-4000 cps, and 4000 cps (see, e.g., Example 1; formulations A, B, and C). Finally, as noted above, Wenig teaches that "more viscous compositions even up to 10,000 cps may be employed."

The evidence of record therefore directly refutes the Office's interpretation stating that:

> The motivation to combine these references is provided by Wenig where it is stated that the important point is to use an amount of thickening agent that will achieve the selected viscosity. . . . Further, if the one skilled in the art were interested in forming a solution rather than a gel, the viscosity could be decreased in a manner as suggested by Wenig while maintaining the formulation with the humectants, preservative and cyanocobalamin as found in the Wenig patent. (Office Action at pp. 4-5).

The purported motivation to combine references attributed to Wenig by the Office is contrary to the express teachings of Wenig noted above. There is absolutely no support in the record for the proposition that "viscosity could be decreased *in the manner suggested by Wenig*." (emphasis added). No such suggestion is provided by this primary reference, which instead expressly teaches a minimum contemplated viscosity of "2500 to 6500 cps, although *more viscous compositions even up to 10,000 cps may be employed.*" (*supra*). Of course, viscosity of any aqueous gel formulation "could be decreased", by any of a number of possible manipulations, but no such teaching nor suggestion is found in the disclosure of Wenig, whereby the record is insufficient to validate the asserted grounds for rejection.

The relevant inquiry for the Office to make in considering these facts is whether Wenig provides direct, "practical" motivation that would have led the ordinarily skilled artisan to modify a cyanocobalamin gel formulation to lower the viscosity to "less than about 1000 cPs"—as expressly averred by the Office. Wenig clearly fails to teach or

suggest that it would be desirable, for any purpose, to decrease the viscosity of an intranasal cyanocobalamin gel formulation to arrive at the formulations presently claimed by Applicants. As noted above, Wenig fails to practically motivate the artisan to develop an intranasal cyanocobalamin formulation according to Applicants' claims (e.g., having a viscosity of "less than about 1000 cps"), and in fact expressly teaches away from such modification. The only teachings of Wenig that relate to the subject of "adjusted" or "selected" viscosities for an effective intranasal cyanocobalamin formulation, expressly limit viscosity selection/adjustment to a critical, minimum range of "from about 2500 to 6500 cps", and the only direction for departure from this minimum range is expressly indicated to be toward "more viscous compositions even up to 10,000 cps". These antithetical teachings correspond in "practical" terms to a narrow range of working embodiments provided by Wenig, which constitute a small assemblage of formulations validated by blood plasma B_{12} measurements having a narrowly limited viscosity range of between 3500-4500 cps (*supra*).

The Office expressly attributes the alleged "motivation to combine" the teachings of Wenig, Garcia-Arieta et al., and Slot et al. in the context of viscosity adjustment to Wenig (*supra*). However, as noted above, Wenig provides no practical motivation nor guidance to decrease the viscosity of an intranasal cyanocobalamin gel formulation (i.e., the primary formulation disclosed by Wenig that is relied upon by the Office). On the contrary, Wenig's disclosure must be considered to teach directly away from this proposed modification.

Similarly, there is no teaching nor suggestion provided by Wenig to substitute an aqueous liquid (spray or drop) cyanocobalamin formulation for the disclosed intranasal gel formulation of Wenig. No direct support for this proposed "format" modification is even asserted by the Office, and the teachings of Wenig noted above directly contravene this proposed format modification. In addition, Wenig expressly teaches in the background section of the disclosure that non-gel (powder and aqueous) formulations of cyanocobalamin are ineffective for intranasal administration to treat vitamin B_{12} deficiency. With regard to aqueous formulations, Wenig cites, e.g., an aqueous isotonic sodium chloride solution of vitamin B_{12} reported by Monto et al. (Am. J. Med. Sci.

223:113, 1953; Arch. Int. Med. 93:219, 1954). As reported by Wenig, this solution, along with powdered cyanocobalamin formulations, are ineffective for intranasal use to treat vitamin B_{12} deficiency, because:

> [M]ost of the B_{12} passes immediately into the throat. It is not in contact with the nasal mucosa for a sufficient period of time to permit useful and uniform absorption. Most of the B_{12} so administered is, in fact wasted. (Col. 1, lines 63-68).

Thus, the primary reference relied upon by the Office (to which the principal "motivation to combine" formulation parameters is attributed), not only teaches away from decreasing viscosity of an intranasal cyanocobalamin formulation below a critical, minimum range of 2500-6500 cps, but also expressly negates the proposed modification to substitute an aqueous (spray or drops) composition for Wenig's intranasal gel formulation. Wenig provides clear evidence and reasoning that teaches directly away from such a proposed modification. In particular, Wenig teaches that effective intranasal cyanocobalamin formulations must have "a sufficient amount of a thickening agent so that the viscosity is from about 2500 to 6500 cps" (*supra*)—which Wenig describes as a critical parameter to render the formulations "sufficiently viscous to maintain themselves in the nasal passages for a period of time which is long enough so that most of the B_{12} is absorbed." (Col. 2, lines 24-29). These properties are directly contrasted by Wenig to the properties of non-gel (liquid and powder) cyanocobalamin compositions, which, according to Wenig's express teachings, fail to exhibit sufficient nasal mucosal residence time to achieve effective intranasal delivery/bioavailability of cyanocobalamin. The Office provides no contrary evidence that would refute or overcome these teachings to validate the instant rejection.

Further in regard to the proposed modification of Wenig to lower viscosity and/or substitute a liquid instead of a gel "format", the Office cites Garcia-Arieta et al. for allegedly teaching "the nasal administration of cyanocobalamin in nasal solution (spray and drops) as well as the bioavailability of this formulation." (Office Action, at p. 5). Applicants respectfully submit that the Office's interpretation of this reference is clearly in error. In particular, Garcia-Arieta et al. describes "Spray-Dried Powders as Nasal

Absorption Enhancers of Cyanocobalamin" (Title). The only disclosure by Garcia-Arieta et al. with regard to any cyanocobalamin spray and drop formulation is derived from a comparative experiment, from which the authors expressly report that liquid (spray and drop) cyanocobalamin compositions are inoperable for intranasal use.

More specifically, Garcia-Arieta et al. tested bioavailability of three spray-dried, intranasal cyanocobalamin formulations alongside two experimental cyanocobalamin nasal solutions (drops and spray containing 0.1% cyanocobalamin; no other formulation parameters specified) (p. 1412, right column). In contrasts to the Office's allegation that Garcia-Arieta et al. teach "the bioavailability" of these formulations, the reference unambiguosly reports that the experimental nasal spray and drop formulations of cyanocobalamin yielded no detectable bioavailability whatsoever. As reported at page 1415, left column, Garcia-Arieta et al. found from their experiments that:

> [N]either the nasal solution in drops nor in spray were able to increase the basal level of serum cobalamin in rabbits to a statistically significant level. This means that either the cyanocobalamin is hardly absorbed by the nasal route when it is administered without absorption enhancers *or that due to the lack of any viscosity-enhancing agent these formulations were not retained in the nasal cavity for long enough to allow their absorption.* (emphasis supplied).

These experimental findings directly demonstrate inoperability of an aqueous, low viscosity cyanocobalamin formulation, which accords closely with the conclusions by Wenig noted above. Accordingly, both the primary and principal secondary references relied upon by the Office expressly teach that non-gel, liquid intranasal formulations of cyanocobalamin would have been predicted to be ineffective to achieve useful therapeutic results. These references therefore independently and collectively refute the Office's position that it would allegedly have been obvious to modify an intranasal cyanocobalamin gel formulation according to Wenig by decreasing the viscosity and/or substituting a liquid (spray or drop) "format" for Wenig's high-viscosity gel formulation.

As noted above, Wenig expressly contravenes both of these proposed modifications by disclosing a critical threshold viscosity above 2500 cps, and a much higher range of 3500-4500 cps for all demonstrated working embodiments. Garcia-

Arieta et al. provides yet additional (direct experimental) evidence that 1% cyanocobalamin spray and drop formulations yielded no detectable bioavailability--which the authors attribute to either a lack of absorption enhancing (powder) agents, and/or insufficient viscosity.

The Office's reliance on Slot et al. as a secondary reference appears to be limited to the subject of preservatives. The Office cites Slot et al. for the limited alleged teaching of "an intranasal formulation of hydroxocobalamin preserved solution". (Office Action, at p. 4). No further explanation is provided regarding the asserted significance of Slot et al. to support the instant rejection. In the same passage that Slot et al. is discussed, the Office refers to both Garcia-Arieta et al. and Slot et al. in a generalized and vague context, asserting that:

> The exact concentration of preservatives, humectants and cyanocobalamin are not taught by either of these references, however, one skilled in the art of pharmaceutical formulations would be able to optimize such formulations with the humectants, preservatives and cyanocobalamin to modulate the viscosity and pH to obtain a therapeutically useful formulation. (Office Action at p. 5).

Without further clarification by the Office, Applicants can neither determine nor address these asserted secondary grounds for rejection. Applicants respectfully submit in this context that the Office has not met its burden of articulating specific, detailed grounds for rejection to establish that each and every element and limitation in the rejected claims is either disclosed, or directly suggested, among the cited references. It is insufficient for the Office to assert that Slot et al. allegedly discloses "an intranasal formulation of hydroxocobalamin preserved solution", and to infer from this limited evidence that all terms and limitations in Applicants' claims relating to preservatives would be obvious based on a non-specific motivation "to optimize such formulations"--with no mention or specific reference teachings, parameters, values, etc.

These same insufficiencies are submitted to be apparent with regard to the selection and concentration of cyanocobalamin as an active agent in an effective intranasal liquid formulation for treating vitamin B_{12} deficiency. Regarding this subject

matter, Slot et al. expressly teach that hydroxocobalamin is the preferred form of vitamin B_{12} for treating vitamin B_{12} deficiency, and that cyanocobalamin is not an effective or practical treatment agent for use in liquid, intranasal delivery formulations or methods. Like Wenig, Slot et al. comment on a previously-described, isotonic saline solution of cyanocobalamin, stating that:

> [N]one of these proposals found a follow-up in clinical practice. Apparently the results were not very practical. (page 432, right column).

Slot et al. further teach away from Applicants' intranasal cyanocobalamin formulations and methods, by disclosing that:

> Hydroxocobalamin binds more extensively to plasma proteins and has a longer half time in the body than cyanocobalamin. As a result, hydroxocobalamin is better retained in the body and, therefore, requires less frequent dosing. Moreover, cyanocobalamin is contraindicated in patients with tropical amblyopia and simultaneous tobacco usage and in patients with pernicious anemia with optic neuropathy; hence, hydroxocobalamin is the drug of choice in restoring vitamin B_{12} deficiencies. (page 432, right column).

Another reference of record that teaches away from the selection of cyanocobalamin as a useful form of cobalamin in intranasal formulations and methods is Merkus, USPN 5,801,161. Similar to the teachings of Slot et al., Merkus expressly states that hydroxocobalamin is a preferred treatment agent for vitamin B_{12} deficiency in comparison to cyanocobalamin. In the specific context of nasal formulations, Merkus emphasizes that:

> [T]he most effective concentrations of vitamin B_{12} in the formulations for nasal administration are higher than 1%. The maximal concentration that can be reached with cyanocobalamin is about 1%. Concentrations above 1% can only be obtained with hydroxocobalamin, because its good solubility in water. The solubility of hydroxocobalamin substances can be as high as 10%, which means that up to about 10 times more vitamin B_{12} per unit of volume can be administered and subsequently

> absorbed nasally, when hydroxocobalamin is used. (Col. 3, lines 43-53)

In view of the foregoing evidence, the art of record strongly teaches away from the selection of cyanocobalamin as a useful agent within liquid, intranasal formulations and methods to treat vitamin B_{12} deficiency. Based on these teachings, the record is even more clear that persons of ordinary skill in the art would not have found practical motivation among the art of record to independently develop Applicants' novel, low viscosity cyanocobalamin formulations and methods.

To establish such practical motivation, the Office must not only show a direct suggestion among the cited references to make all of the proposed modifications necessary to arrive at Applicants' claimed invention, but the evidence provided must be sufficient to show that those modifications would be reasonably expected to yield similar results as disclosed by Applicants. As the Federal Circuit held in Interconnect Planning Corp. v. Feil, it is "critical" for determining obviousness that the Office consider "the particular results achieved by the new combination . . . ." 227 USPQ 543 (Fed. Cir. 1985). As further explained in In re Merck, 231 USPQ 375, 379-80 (Fed. Cir. 1986):

> [T]he governing standard is emphatically not whether a particular methods or process leading to an invention would be "obvious to try", but whether such an experiment would have been expected to succeed.

To determine what constitutes a "reasonable expectation of success" in this context, the Federal Circuit's predecessor court held in In re Gyurik, 201 USPQ 552, 557 (CCPA 1979) that:

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.

Applying this authority to the present facts, there is insufficient motivation and guidance identified by the Office to support the instant rejection under 35 USC § 103.

On the contrary, the evidence presented above establishes that persons of ordinary skill in the art would not have been practically motivated to develop Applicants' novel, low viscosity cyanocobalamin formulations. The art of record fails to establish any reasonable expectation that Applicants formulations and methods could be developed and employed to successfully achieve therapeutically effective delivery/bioavailability of cyanocobalamin sufficient to alleviate vitamin B12 deficiency, as disclosed by Applicants. More specifically, the art of record fails to evince practical motivation coupled with a reasonable expectation for developing the instant formulations and methods specifically characterized as providing a bioavailability "when administered intranasally of at least about 7% relative to an intramuscular injection of cyanocobalamin."

The lack of practical motivation and guidance to satisfy these criteria to sustain a *prima facie* obviousness case is clearly supported by the evidence and reasoning above. Contrary to the Office's position, the art of record expressly teaches away from the core aspects of Applicants' invention. To properly interpret this evidence, Applicants' respectfully direct the Office's attention to the Federal Circuit's holding in In re Gurley, 31 USPQ2d 1130, 1131 (1994), where the panel held that, as a "useful general rule", "a reference that 'teaches away' can not serve to create a prima facie case of obviousness..

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the (application), or would be led in a path divergent from that taken by the applicant.
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> [I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. (Id.)

Considering this authority, both Wenig and Garcia-Arieta et al. teach directly away from Applicants' low viscosity liquid cyanocobalamin formulations. Wenig expressly teaches a critical, minimum viscosity for an effective, intranasal cyanocobalamin between 2500-4000 cps. Both Wenig and Garcia-Arieta et al. teach that non-gel, liquid cyanocobalamin formulations would not be expected to be retained for a

sufficient time to allow for intranasal absorption. Garcia-Arieta et al. specifically report experimental results that no significant bioavailability was detected following nasal administration of a 1% liquid cyanocobalamin formulation.

Similarly with regard to the selection and concentration of cyanocobalamin as an active form of cobalamin for use in an intranasal liquid formulation, Slot et al. and Merkus collectively teach that cyanocobalamin would be expected to be ineffective, or at best strongly disfavored in comparison to hydroxocobalamin, in an intranasal formulation for treating vitamin B_{12} deficiency (independent from viscosity considerations). Exemplifying these teachings, Merkus emphasizes that:

> A high and efficient intranasal absorption of vitamin B_{12} is advantageous in medical therapy and can be obtained only by using hydroxocobalamin, which shows a significant higher solubility in water than cyanocobalamin. Only with hydroxocobalamin a superior nasal composition in an aqueous medium can be produced with by far the highest concentration of vitamin B_{12} and consequently a much more efficient nasal absorption of vitamin B_{12}. Such a nasal formulation can be taken less frequently by patients, making the therapy much easier and less expensive. (Col. 2, lines 27-37).

These collective teachings clearly establish that the art of record teaches a "path divergent from that taken by the applicant", and that "the reference's disclosure is unlikely to be productive of the result sought by the applicant" (in this case, the "particular results" disclosed by Applicants, which must be fully considered by the Office, encompass low viscosity cyanocobalamin compositions and methods that are effective for intranasal use, specifically yielding at least 7% relative bioavailability compared to intramuscular administration).

In view of the foregoing evidence and authority, Applicants respectfully submit that the primary factual assertions presented by the Office regarding formulation ingredients and parameters allegedly disclosed by Wenig in view of Garcia-Arieta et al. and Slot et al. are incorrect, and that these references neither teach nor suggest the novel cyanocobalamin formulation particulars of the current kit and method claims.

On this basis, Applicants submit that the additional modifications proposed by the Office (i.e., to modify a cyanocobalamin formulation as claimed by adding additional "devices and parameters" according to Grychowski et al. and Harris et al.) need not be addressed. The foregoing evidence and authority pertaining to formulation aspects of the claims clearly distinguish the primary subject matter relied upon by the Office to support the rejection, whereby it is clear that no further combinations employing devices and related parameters would yield a combination reading on the instant claims. Nonetheless, Applicants will briefly address the secondary combinations proposed by the Office, below.

The Office asserts that it would have been obvious to modify a cyanocobalamin formulation as set forth in Applicants' claims by employing additional "devices and parameters" to yield kits and methods. In particular, the Office cites Grychowski et al. for allegedly teaching "an intranasal device that can be characterized as a kit that contains a container and an actuator." The Office further cites Harris et al. for allegedly teaching that "viscosity, particle size, and nasal clearance are important parameters in the design of nasal delivery systems." On these limited grounds, the Office proposes that:

> [O]ne who is skilled in the art of nasal drug delivery systems would readily know what parameters to adjust to optimize a nasal formulation of cyanocobalamin. For example, one skilled in the art would readily be able to adjust the spray pattern ellipticity ratio, droplet size and spray pattern major and minor axes by selecting different tips as found in Grychowski et al and adjusting the parameters as taught by Harris et al.

These secondary grounds for rejection asserted by the Office notably make no mention of the specific parameters and characteristics of Applicants' kit and method claims. The actual "devices and parameters" taught by Grychowski et al. and Harris et al. are wholly ignored. Consequently, the rejection amounts to a blanket dismissal of all conceivable nasal delivery technologies directed to novel combinations of spray pattern ellipticity ratios, droplet size ranges, and spray pattern major and minor axes parameters, for all conceivable intranasal compositions, including all possible forms and format of cobalamin.

This blanket dismissal clearly fails to satisfy the Office's burden to show that every element and limitation in each of Applicants' rejected claims is either directly disclosed, or is specifically suggested by the cited references. According to the above-cited authority, such suggestion must be "practical", and must be directly "related to the properties or uses one skilled in the art would expect the (formulations/kits/methods) to have, if made". The Office must not only show direct suggestions among the cited references to make all of the proposed modifications necessary to arrive at Applicants' invention, but must establish that skilled artisans would have practically followed those suggestions with an expectation of arriving "the particular results" disclosed by Applicants.

Applying this authority to the present facts, there is insufficient motivation and guidance identified by the Office among the cited references to support the further combination of "devices and parameters" found in Applicants' kit and method claims. These claims specifically recite novel and distinct aspects of the invention pertaining to spray pattern ellipticity (about 1.0-1.4 at a height of 3.0 cm from tip of actuator; claims 1, 14, 18, 29, and 35); droplet size/distribution (maximum size/percentage as specified in claims 2, 4, 11-13, 15-18, 21, 28-30, 32-35, and 38-41); and spray pattern major axis and minor axis values (25-40 mm, respectively, in claims 5, 22, 36, and 42; about 35.3 in claim 19) values.

None of the foregoing specific technical features is identified or in any way suggested by the art of record. On the contrary, Grychowski et al. teach various structural aspects of a nasal delivery device, but make no specific mention of functional parameters within Applicants' claims that can be practically achieved by the various, specific actuator tips described. There is therefore no basis in this reference to support the Office's blanket assertion that all of Applicants' specific spray pattern ellipticity, droplet size/distribution, and spray pattern major axis and minor axis values for a cyanocobalamin formulation (having the indicated viscosity and other formulation parameters), could be achieved simply "by selecting different actuator tips as found in Grychowski et al." (Office Action at p. 3). Even if this ready selection were in fact possible (which can in no way be discerned based on the limited teachings of Grychowski

et al.), the record clearly lacks foundation to support the Office's contention that Grychowski et al. and Harris et al. specifically suggest, and practically motivate, selection of the specific, novel combinations of spray parameters as instantly claimed.

In this context, the only performance criteria referenced by Grychowski et al. actually teach away from the present claims. In particular, Grychowski et al. teach limited, and clearly distinct, values for the major and minor axes of the spray pattern produced by the subject device actuator tips. Whereas Grychowski et al. specifically limit their major and minor axes values to between 40-70 mm, and 25-40 mm (preferably 58 mm, and 32 mm) (Col. 8, lines 16-21), respectively, both of Applicants' major and minor axes have the identical expressed range of between 25-40 mm (or more specifically, about 35.3 mm). In this regard then, Grychowski et al. not only fail to teach or suggest Applicants' specified values for spray pattern major and minor axes, but expressly teach away from these values for all of the described embodiments of a nasal spray device.

Grychowski et al. make no mention whatsoever of specific desired particle size/distribution values as recited in Applicants' claims. All that this reference teaches in this context is that "[o]ne of the more significant problems with nasal sprayers is nasal drip and oral ingestion", and that this problem may be "caused by particles that are too large to be absorbed by the targeted nasal area." (Col. 1, lines 29-33). This general teaching clearly fails to support the Office's position that "by selecting different actuator tips as found in Grychowski et al." the artisan could readily arrive at any conceivable spray particle size/distribution, for any cyanocobalamin formulation (irrespective of such additional formulation parameters such as viscosity) as the rejection indicates. Moreover, even if selection of a device according to Grychowski et al. could, conceivably, yield the subject spray particle size/distribution, the record is devoid of any specific teachings that would suggest the specific parameters claimed by Applicants.

Finally, Grychowski et al. makes no mention of spray pattern ellipticity, nor does the reference suggest that different application tips described therein could be selected to achieve different spray pattern ellipticity values, particularly values corresponding to those recited in Applicants' claims.

With respect to Harris et al., this reference teaches nothing about devices and spray pattern parameters that would complement or cure the deficiencies of Grychowski et al. noted above. In this context, Harris et al. only generally address the subject of particle size, and make no mention of the other spray parameters recited in Applicants' claims. The teachings of Harris et al. most closely pertain to a proposed relationship between particle size and dosing accuracy, deposition and clearance for nasal delivery systems, and how particle size might be adjusted by changing viscosity of a nasal formulation. The studies of Harris et al. are all based on a distinct formulation (an aqueous methylcellulose preparation), and, most importantly, yielded conclusions that teach directly away from Applicants' novel viscosity and particle size/distribution values.

In particular, Harris et al. generally describe that increasing viscosity of a nasal formulation yields a desired increase in particle size, up to an optimal viscosity/particle size that lies well beyond the terms recited for Applicants' novel kits and methods. More specifically, Harris et al. expressly state that "an optimum mean particle size diameter seems to lie in the region of 59-80 μm" (page 407, right column). To support their conclusions regarding "optimum" particle size/viscosity, Harris et al. also cite to a study by Illum (Arch. Pharm. Chem. 94:127-135, 1987), which reportedly "showed that the administration of hydrogels comprising starch or dextran microspheres of mean diameter 60 μm gave a prolonged in vivo retention time compared to conventional powder and liquid nasal formulations." (Id.)

On this basis, Harris et al. (and the cited reference by Illum) must be considered to teach directly away from Applicants' claimed particle size and viscosity values. While viscosity limitations are addressed in more detail above, the specific recitation of particle size/distribution in Applicants' claims (see claims identified above), which were challenged by the Office in view of the "devices and parameters" allegedly taught by Grychowski et al. and Harris et al., is neither disclosed nor suggested by the art of record. In fact, by teaching an "optimum" particle size of "59-80 μm" (well above the highest values expressed in the pending claims), and linking these high particle size values to high viscosity formulations, Harris et al. wholly contravenes the Office's position.

In view of the foregoing, Applicants respectfully submit that the rejection of claims 1-16 under 35 USC § 103(a) as allegedly unpatentable over Wenig (USPN 4,724,231), Grychowski et al. (USPN 6,745,760), Slot et al. (Gastroenterology 113:430-433, 1997), Garcia-Arieta et al. (Biol. Pharm. Bull. 24:1411-1416, 2001), and Harris et al. (J. Pharm. Sci. 77:405-408, 1988) should be withdrawn.

Claims 20-42 are rejected under 35 USC § 103(a) as allegedly unpatentable over Wenig (USPN 4,724,231), Grychowski et al. (USPN 6,745,760), Slot et al. (Gastroenterology 113:430-433, 1997), Garcia-Arieta et al. (Biol. Pharm. Bull. 24:1411-1416, 2001), and Harris et al. (J. Pharm. Sci. 77:405-408, 1988).

To support this rejection, the Office relies upon the same prior art teachings addressed above, allegedly "relating to the compositions from which the methods depend therefrom" (Office Action at p. 7). However, the subject, dependent method claims all depend from independent method claim 20. They are thus collectively independent from the previously-addressed composition claims.

The Office further asserts that the art of record teaches "[a]ll of the intranasal drug delivery devices, parameters for adjusting the spray pattern ellipticity ratios, droplet sizes and spray pattern major and minor axes as well as formulation ingredients" (Office Action at p. 7). From this conclusory statement (which has been extensively refuted above), the sole additional basis for the rejection of method claims offered by the Office is the assertion that "the nature of the formulation ingredients are correlative with the methods as found in the prior art.

Applicants neither understand, nor accede to, the merits of this blanket rejection of method claims--based solely on common formulation and structural elements and limitations with Applicants' kit claims. The alleged prior art disclosure of all formulation ingredients and parameters, and of all intranasal drug delivery devices and spray parameters is neither founded in the context of the above-addressed kit claims, nor directly related to the independent method claims (for which no prior art "methods" are even identified--apart from what might be inherent based on the cited references). The Office does not undertake to explain how one or more (unspecified) prior art methods might be practically combined to read, alone or in combination, on Applicants' claimed

methods. Thus, the rejection is respectfully submitted to be improper, or at best incomplete and prejudicial to a full and reasoned response.

Because the instant rejection is founded on the limited basis of prior art teachings relating to Applicants' kit claims, which are fully addressed above, no additional remarks are believed necessary, or further responsive, here.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 908-3600

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Respectfully submitted,

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